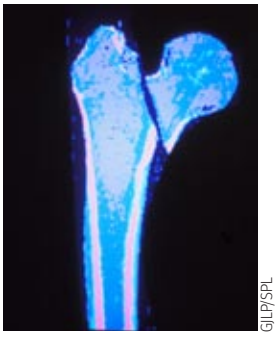
Reducing the risk of fractures with calcium and vitamin D

The combination is more effective than vitamin D alone



GJLP/SPL

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CLINICAL REVIEW, p 142

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Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;339:b5492
doi: 10.1136/bmj.b5492

Conflicting evidence exists on the role of vitamin D, either alone or in combination with calcium, in reducing fractures. Some studies have shown a reduction in the risk of fractures, others have shown no effect, and one recent study found an increased risk of hip fracture.[1] The best dose to use, which patients benefit most, and which fractures are most amenable to such treatment remain a clinical dilemma.

In the linked study, the DIPART (vitamin D Individual Patient Analysis of Randomized Trials) group reports an individual patient data analysis aimed at identifying factors that influence the efficacy of vitamin D or vitamin D plus calcium in reducing fractures. The study also assessed the influence of dosing regimens and the coadministration of calcium. The study looked at seven randomised controlled trials (n=68 517)—six were individually randomised and one was cluster randomised.[2] It found that trials using vitamin D (low or high dose) combined with calcium reduced the overall risk of fracture (hazard ratio 0.92, 95% confidence interval 0.86 to 0.99), but that only low dose (10 µg) vitamin D combined with calcium reduced the risk of hip fracture (0.74, 0.60 to 0.91). They found no association between fracture history and treatment response, or any association with age, sex, or hormone replacement therapy. In addition, vitamin D alone, irrespective of dose, had no effect on fracture risk.

These findings are important because this is one of the few individual patient data analyses to show that vitamin D alone, irrespective of dose, does not reduce the risk of fracture. In contrast, it found that combined calcium and vitamin D reduced the overall risk of fracture, but that only low dose vitamin D with calcium reduced the risk of hip fracture.

The DIPART group's analysis supports recent meta-analyses that have examined study level data rather than individual patient level data.[3 4] One of the recent meta-analyses based on study level data found that although a combination of calcium and vitamin D prevented the overall risk of fracture, it was only significant in people living in institutions. The conclusions were mainly driven by a large French study, which the DIPART study did not include.[5]

Another recent study level meta-analysis by Bischoff-Ferrari and colleagues of 12 randomised controlled trials of non-vertebral fractures (n=42 279) and eight trials of hip fracture (n=40 886) looked at oral vitamin D, with or without calcium.[6] It concluded that prevention of non-vertebral fractures with vitamin D was dose dependent. Ten of the included studies were not included in the DIPART group's review and two of the studies that were included in the DIPART group's review were not included in Bischoff-Ferrari and colleagues' review. Furthermore, in two studies of higher dose vitamin D that were included in the DIPART group's study, compliance with treatment was poor. Bischoff-Ferrari and colleagues' analysis adjusted for compliance by multiplying the dose by the percentage of adherence to estimate the mean received dose for each trial. The DIPART group made no such adjustment, which may explain the contrasting conclusions between the two meta-analyses.

For many years, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) were believed to have equivalent effects on the human body, even though differences in the metabolism of these two forms were seen in animals 25 years ago. Some studies have suggested that supplemental vitamin D_2 is less effective than vitamin D_3 in humans[7]; however, in the meta-analysis by Bischoff-Ferrari and colleagues, subgroup analyses suggested that vitamin D_3 may be better at reducing fractures than vitamin D_2. In contrast, the results of the DIPART study were similar regardless of whether the potency of vitamin D_2 was considered to be 100% or 50% of vitamin D_3. The optimal concentration of the main circulating form of vitamin D, 25-hydroxyvitamin D, is still debated. Recent consensus has suggested that serum concentrations of 70-80 nmol/l are needed for normal health.[8] However, few vitamin D studies have measured 25-hydroxyvitamin D concentrations, and in those that have such high values are rarely achieved. In addition, the different assays used to measure vitamin D have a limiting effect.[9]

More recently there has been interest in the relation between vitamin D and muscle function. Vitamin D has direct effects on muscle strength modulated by specific vitamin D receptors in human muscle tissue.[10] It is postulated that supplementation may increase muscle strength, thereby reducing the risk of falls and subsequent non-vertebral fractures. In a recent meta-analysis, supplementation with 700-1000 IU of vitamin D a day reduced the risk of falling in older people by 19%, and to a similar degree to active forms of vitamin D.[11] In combination with calcium, vitamin D reduced first falls by 27% at 12 months (relative risk 0.73, 0.54 to 0.96) and 39% at 20 months, with a 28% decrease in body sway.[12] Thus, the reduction of non-vertebral fractures may be related more to the effects of vitamin D on reducing falls than to its direct effects on bone.

What are the implications of current evidence in clinical practice? Although the evidence is still confusing, there is growing consensus that combined calcium and vitamin D is more effective than vitamin D alone in reducing non-vertebral fractures. Higher doses are probably necessary in people who are more deficient in vitamin D, and treatment is probably more effective in those who maintain long term compliance. Further studies are needed to define the optimal dose, duration, route of administration, and dose of the calcium combination.

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Prevention of lymphoedema after axillary surgery for breast cancer

Physiotherapy shows promise in a selected group of women

RESEARCH, p 140

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Competing interests: The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouse, partner, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;339:b5235
doi: 10.1136/bmj.b5235

Lymphoedema is a potential complication of the treatment of primary breast cancer that reduces the quality of life of millions of breast cancer survivors.[1] Cure is not possible and patients have a life long dependence on compression garments and other labour intensive treatments to prevent worsening of the condition's hallmarks—arm swelling and discomfort.

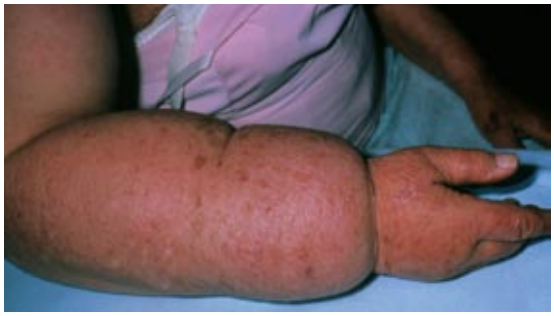
The recognition that more extensive surgery and radiation substantially increase a woman's risk of developing lymphoedema has spurred on the development of treatments that lessen lymphatic injury, such as sentinel lymph biopsy.[2] Nevertheless, about a third of patients with breast cancer present with lymph node positive disease and cannot benefit from these treatments because they need surgical clearance and perhaps irradiation of their axillary lymph nodes.[3] As many as 60% of patients who undergo axillary lymph node resection and irradiation will eventually develop lymphoedema.[4] Therefore, an intervention that could reduce the risk of lymphoedema after treatment would be an important advance. None is presently known.

In the linked study,[5] Lacomba and colleagues report a randomised controlled trial that assessed the effectiveness of the early application of physiotherapy on secondary lymphoedema in 120 women who had surgery for breast cancer (including axillary lymph node dissection).[2] The authors found that significantly fewer women receiving physiotherapy developed clinically important lymphoedema at one year compared with controls (25% *v* 7%; risk ratio 0.28, 95% confidence interval 0.10 to 0.79).

However, several factors should be considered when generalising the results to clinical practice. Firstly, physiotherapy can be highly tailored, particularly for treatments involving the manual components (for example, massage) included in Lacomba and colleagues' study. The therapists in this study had more than five years' experience in treating vascular diseases and in lymphatic drainage, but few physiotherapists have comparable experience. Treatment techniques vary even among therapists with well developed skills in lymphatic drainage. Readers should therefore not assume that women with breast cancer who are referred for physiotherapy will necessarily receive similar treatment or achieve similar results to those in Lacomba and colleagues' study.

The study cannot separate the effects of each component of the intervention—manual lymph drainage, massage of the scar, progressive active and active assisted shoulder exercises, and education. Further research is needed to clarify the relative contributions of each of these components to the prevention of lymphoedema and to inform the specifics of future physiotherapy programmes, such as frequency, duration, and intensity. For example, the necessity of the time intensive manual treatments included in Lacomba and colleagues' intervention is inconsistent with an earlier trial which found that lymphoedema was reduced by a predominantly educational intervention.[6]

An additional consideration is the practical need to restrict treatment to women most at risk of developing lymphoedema. Only about 5-7% of people who undergo sentinel lymph node biopsy without surgical clearance of the axillary lymph node develop lymphoedema.[7] So



DR P MARAZZI/SPL

Lymphoedema following radiotherapy treatment for breast cancer

large numbers of patients would need physiotherapy to prevent a single case of lymphoedema. The situation is very different for patients who undergo surgical clearance and irradiation of axillary lymph nodes—only a few would require physiotherapy to have a clinically meaningful benefit. Lacomba and colleagues acknowledged this fact by only recruiting women who needed surgical resection of their axillary lymph nodes. The recent finding that lymphoedema in breast cancer survivors increases annual healthcare costs unrelated to cancer by an average of £4500 (€5000; $7500) per patient per year suggests that giving physiotherapy to patients at high risk of lymphoedema may reduce costs.[8]

The benefits of physiotherapy after treatment for breast cancer extend well beyond the prevention of lymphoedema and include the restoration of the complete range of shoulder movement, normalisation of upper quadrant biomechanics, and pain control. These are not trivial benefits. For example, a recent report noted that almost half of 3253 survivors of breast cancer had moderate or severe regional pain two to three years after treatment.[9] Another study reported a similarly high prevalence of pain and also that disease-free survivors who had surgical axillary lymph node clearance remained limited in terms of their shoulder movements and upper extremity function for prolonged periods.[10] Physiotherapy has been shown to reduce the incidence and severity of these problems in several well powered randomised controlled trials.[11-13]

Lastly, follow-up in Lacomba and colleagues' study was limited to 12 months; we do not know if the intervention prevented or simply delayed lymphoedema. If physiotherapy facilitated repair of damaged lymphatics or removed barriers to normal healing—for example, lessened fibrosis, then the benefit may be sustained indefinitely. Alternatively, physiotherapy may have simply delayed rather than prevented the onset of lymphoedema, possibly by reducing lymphatic overload through strengthening activities. Trials with longer term follow-up are needed to answer this question.

Limited but compelling evidence supports the usefulness of physiotherapy after surgical clearance of the axillary lymph nodes to control pain, enhance shoulder functionality and range of motion, and reduce a woman's risk of developing lymphoedema. Clinicians should therefore consider referring patients to physiotherapists who are trained in treating lymphoedema. Future research is needed to assess the efficacy of specific treatment modalities such as education and manual lymphatic draining.

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Antihypertensive agents and prevention of dementia

It is plausible that some of these drugs cut dementia risk

RESEARCH, p 141

Cite this as: *BMJ* 2009;339:b5235
doi: 10.1136/bmj.b5235

About 36 million people worldwide have a form of dementia such as Alzheimer's disease. If survival, prevention, or treatment do not improve dramatically, this number could double over the next 20 years.[1] In the search for interventions to delay or prevent this condition, vascular risk factors have attracted attention. Various studies have shown an association between mid-life hypertension (especially if untreated) and the likelihood of developing dementia,[2 3] raising the possibility that antihypertensives might offer an effective form of prevention.

In the linked study, Li and colleagues report on the possible role of angiotensin receptor blockers in reducing the risk of dementia and slowing progression.[4]

Several prospective cohort studies show an association between pharmacotherapy for hypertension and a lower risk of cognitive decline or incident dementia (in people under 75 years).[3 5] Patients with Alzheimer's disease treated with antihypertensives seem to have better cognitive outcomes.[6] With a few exceptions,[5] these observational studies assessed only baseline drug exposure and did not examine the duration of treatment or changes over time. Other concerns include limited study duration, selective loss to follow-up, and confounding by indication. In addition, failure to have a long enough latency

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

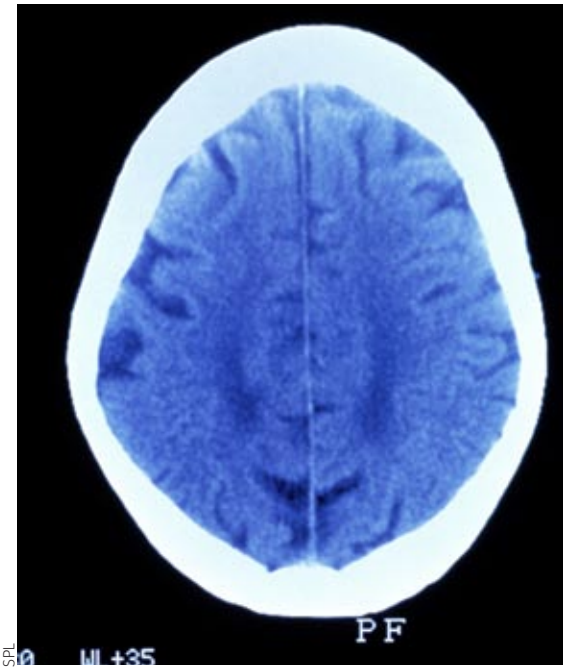
Provenance and peer review: Commissioned; not externally peer reviewed.

period before the diagnosis of dementia when assessing drug exposure can lead to a protopathic bias. This means that early unrecognised disease manifestations such as a reduction in blood pressure, apathy, or impaired cognition may reduce the likelihood of starting or continuing treatment and may result in a spurious protective effect.

Cell based research and animal models suggest several biological mechanisms by which antihypertensives might be neuroprotective. In addition to lowering blood pressure and reducing vascular pathology, certain agents may have an effect on the neuropathology of Alzheimer's disease.[7] Biological plausibility, however, does not equate to clinical effectiveness. If there is a protective effect, it is unclear whether this results from a reduction in blood pressure or, at least in part, some other mechanism. If the first scenario is true, we should focus on lowering blood pressure by whatever effective means, but if the second is true we should be careful in our choice of agent.

Randomised controlled trials of antihypertensives in later life that have cognition as an outcome show mixed results. Only the Systolic Hypertension in Europe (Syst-Eur) study showed a significantly lower incidence of dementia with active treatment.[8] Other trials found no overall benefit, although some subgroups (such as patients with mild cognitive impairment at baseline or recurrent stroke) had improved outcomes. Common criticisms include their relatively short duration, enrolment of low risk (from a cognitive standpoint) subjects, treatment of cognition as a secondary outcome, unbalanced numbers of dropouts, and contamination. Meta-analyses have yielded equivocal results.[9 10] Therefore, although results have been promising, the case remains open as to whether treatment of hypertension in later life delays or prevents dementia.

In the linked prospective cohort study of older (over 65), mostly (98%) male, subjects, Li and colleagues found significantly lower hazard rates for incident dementia with angiotensin receptor blockers than with the angiotensin converting enzyme inhibitor lisinopril (hazard ratio 0.81, 95% confidence interval 0.73 to 0.90) and other cardiovascular drugs (0.76, 0.69 to 0.84).[4] In patients with pre-existing Alzheimer's disease, the use of an angiotensin receptor blocker was associated with a lower risk of admission to a nursing home. Both classes of drugs had protective effects that may be additive with concurrent use.



SPL

CT scan of a patient with dementia, showing the effects of multiple infarcts

The reason that angiotensin receptor blockers might be superior to angiotensin converting enzyme inhibitors is that the two receptors have complex and non-identical mechanisms of action. For example, they act differently on type 1 and 2 angiotensin receptors, which are both present in the brain. Stimulation of type 1 receptors causes vasoconstriction, whereas stimulation of type 2 receptors reportedly leads to vasodilation, neuronal differentiation, apoptosis, and axonal regeneration. Angiotensin converting enzyme inhibitors inhibit both receptors, but angiotensin receptor blockers selectively inhibit type 1 receptors. This could translate to improved cerebral blood flow and an enhanced neuroprotective effect. Open label trials of angiotensin receptor blockers suggest beneficial effects on cognition, but two randomised controlled trials (SCOPE and PRoFESS) showed no significant benefit in either the rate of cognitive decline or incident dementia with angiotensin receptor blockers.[11]

Li and colleagues tackled some of the limitations common to observational studies. Similar drug classes were used as comparators, to provide some control for confounding by indication. The comparison with lisinopril seems straightforward, but the cardiovascular comparator contained a broad range of agents with similarly diverse indications. Important confounders such as a family history of dementia, education, and severity of disease were not considered. Although the authors excluded people who presented with dementia in the year before the start of treatment, disease could have been misclassified at baseline and during follow-up, and the potential of protopathic bias with selective initiation or discontinuation of particular antihypertensives remains. Study duration from the standpoint of outcomes was relatively short at four years. As with all studies of this nature, association does not prove causation, and the absence of changes in blood pressure during follow-up further clouds interpretation. The non-random allocation of treatment is also a serious problem. Racial and ethnic disparities in the use of antihypertensives such as angiotensin receptor blockers have been shown among American veterans,[12] and the ethnic origin of most study subjects was not reported. The results may not be generalisable to women, because women comprised only 2% of the cohort.

The public health implications of finding an effective way of preventing dementia are immense, but further work is needed to verify the usefulness of antihypertensives in general and angiotensin receptor blockers in particular.

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Exhaled nitric oxide in the diagnosis of childhood asthma

A small but important piece of the clinical jigsaw

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Competing interests: The authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: (1) no support for the submitted work; (2) no relationships that might have an interest in the submitted work; (3) no spouses, partners, or children with financial relationships that may be relevant to the submitted work; and (4) no non-financial interests that may be relevant to the submitted work.
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;339:b5418
doi: 10.1136/bmj.b5418

Although asthma is the most common chronic disease of childhood,[1] it remains a clinical diagnosis.[2] Common symptoms include recurrent wheezing, cough, difficulty in breathing, and chest tightness, but no agreed "gold standard" definition exists.[2] Improvements in symptoms and lung function seen after adequate treatment often provide retrospective confirmation of the diagnosis.[2]

Accurate diagnosis of asthma in children may be difficult but is vital for two reasons. Firstly, a correct diagnosis is essential for the institution of guideline based treatment, which may involve specialist referral; this is needed to avoid the morbidity and rarely mortality associated with poorly controlled disease.[2] Secondly, the exclusion of asthma prevents potential harm from inappropriate anti-asthma treatment and may highlight other crucial diagnoses such as cystic fibrosis.[3]

Asthma is a heterogeneous disease, and data from large population based studies have informed the concept of different patterns or "phenotypes" in children who wheeze.[4] Importantly, preschool children who wheeze only when they have viral respiratory tract infections form a discrete and largely self resolving group in which wheeze is independent of allergic sensitisation.[4] Wheeze associated with multiple triggers and allergic sensitisation, recognised as the "classic" atopic asthma phenotype, is responsible for most clinically important disease in school aged children but may also be relevant in younger life.[4]

Eosinophilic airway inflammation is the dominant pathology in atopic asthma, and anti-inflammatory drugs are the maintenance treatment of choice.[2 5] However, only a weak correlation exists between airway inflammation and conventional measures of disease status, such as lung function or symptoms.[5] This raises the important question: is it better to assess a child on the basis of improvement of symptoms or lung function or a reduction in inflammation, or even a combination of these?

Some studies in adults with asthma show that treatment aimed at normalisation of sputum eosinophils reduces exacerbations without the need to increase anti-inflammatory drugs.[6] Any extrapolation to children should be done with caution, but it makes sense to try to measure some aspect of airway inflammation to aid clinical decision making.[5-7] Such a test or "inflammometer" should ideally be non-invasive, safe, practical, reproducible, accurate, and cost effective.[7]

Airway eosinophils can be measured in children with the aid of bronchoscopy, so that bronchoalveolar lavage or endobronchial biopsy can be performed, or by the induction of sputum using nebulised saline. Bronchoscopy is invasive and normally requires a general anaesthetic. Induction of sputum requires cooperation from the child and support from laboratory staff. Sputum induction may also provoke substantial bronchoconstriction, and cells from the proximal airway are likely to predominate.[7 8] Nonetheless, the cytology of airway samples may provide evidence of eosinophilic or neutrophilic inflammation that can usefully guide treatment.[8]

Nitric oxide is formed in the airways by a reaction catalysed by nitric oxide synthases.[5] The expression of inducible nitric oxide synthases is increased in inflammation, and the fractional concentration of exhaled nitric oxide (FeNO) is raised in atopic asthma.[5] FeNO has therefore

Best values for fractional concentration of exhaled nitric oxide, sputum eosinophils, and forced expiratory volume in one second[10]

Test	Cut off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
FeNO	19 ppb	86	89	92	80
Sputum eosinophils	2.7%	85	89	92	81
FeNO + eosinophils	19 ppb + 3%	87	89	92	81
FEV_1	80%	52	72	75	48

FeNO=fractional concentration of exhaled nitric oxide; FEV_1=forced expiratory volume in one second; ppb=parts per billion.

attracted a great deal of attention as a potential non-invasive measure of airway inflammation in childhood asthma.[5] In children with atopic asthma, this measure correlates best with eosinophil counts in steroid naive children in sputum or bronchoalveolar lavage but less well with mucosal eosinophils in endobronchial biopsies.[7 9] Importantly, several non-disease factors such as diet, age, race, time of day, and repeatability affect the measurements.[5] Also, FeNO is raised in children with atopy, irrespective of the presence or absence of asthma.[9] This suggests that complex interassociations exist between FeNO, eosinophils, and clinical asthma.[9] However, high FeNO in the presence of symptoms of asthma is suggestive of steroid responsive eosinophilic inflammation.[6]

A recent study measured FeNO and the percentage of eosinophils in induced sputum, in addition to carrying out spirometry, in 150 consecutive white children with a mean age of 12 years, who were referred to a respiratory clinic for evaluation of possible asthma.[10] Children with eczema or allergic rhinitis were included, but those with other "systemic manifestations of atopy," such as food allergy, were excluded. After 18 months of follow-up, 69 children were diagnosed retrospectively by conventional criteria (two or more wheezing episodes documented by a doctor; dyspnoea or cough relieved by bronchodilators; bronchodilator reversibility or variability in lung function over time with or without controller drugs but blind to FeNO and sputum eosinophil results) as having steroid naive asthma, 37 as having asthma already being treated with inhaled corticosteroids, and 44 as not having asthma. The sensitivity, specificity, positive predictive value, and negative predictive value of FeNO and sputum eosinophils depended on the cut-off values used but compared favourably to forced expiratory volume in one second (table). However, application of the best cut-off levels placed 10.6% of children with asthma in an inconclusive "borderline" category. This study was performed in a selected population with a clinical suspicion of asthma. In reality, forced expiratory volume in one second is not considered in isolation from the many other factors used to diagnose asthma.

Advocates for the use of FeNO in childhood asthma argue that the context is crucial, with clinical usefulness being greatest in the specialist clinic.[7] FeNO should be viewed as complementary to conventional history taking, examination, spirometry, and measures of bronchial lability. The history, clinical assessment during an acute episode, and response to anti-asthma treatment are arguably the most valuable criteria in reaching a diagnosis. If several components of the picture are not suggestive then the probability of asthma is reduced. FeNO seems to represent a small but important piece of this clinical jigsaw.

Other possible niches for FeNO include assessment of control, compliance, or the appropriate timing of a reduction in inhaled corticosteroids.[6 11] Crucially, however, well conducted trials of adding the measurement of FeNO to evidence based management of asthma in children and adults have been disappointing, and "getting the basics right" remains paramount in childhood asthma.[12]

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